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EDITORIAL

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Choosing the Right Embryo: The Challenge of the Nineties

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During recent years, the efficiency of in vitro fertilization (IVF) has not increased in a spectacular way despite the use of new methods of ovulation induction such as the luteinizing hormone-releasing hormone (LH-RH) analogues in association with human menopausal gonadotropin (hMG) or embryo freezing. The "take home baby rate" does not—at the majority of IVF centers in the world—exceed 10–12%/cycle, i.e., half the incidence of natural fertility. The waste is impressive. Up to 46 oocytes can be recovered during a single punction but only 10 will be fertilized, and in the end, only 2 will implant. A ridiculous efficiency!

Among all causes of implantation failure, those concerning embryo quality are predominant. Selection of viable normal embryos is therefore the way of the future.

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Numerous articles report on the efforts of scientists to recognize the right embryo. But what is really the right embryo? The concept of the right embryo is easy to define: he should give a viable normal organism that progresses through all the pre- and postimplantation stages. It is, however, more difficult to evaluate. Indeed, the only criteria that can reasonably be applied are those that do not damage the embryo.

Evaluation of the morphological aspect of the embryos, based on the size and regularity of the blastomeres, as well as the presence or absence of cytoplasmic anucleated fragments, proved to be poorly informative except for widely degenerated and fragmented embryos that never lead to pregnancy (1). As morphological criteria were soon found to be of limited value, investigators have attempted to find other methods of evaluation. Chronological criteria seemed to be more reliable: a four-cell embryo obtained 42 hr after insemination has better chances to give a pregnancy than a two-cell embryo (1). Based on embryo scoring and on developmental speed, it is possible to predict pregnancy and even multiple pregnancies (2). It is, however, important to emphasize the limitations of these findings: triploid embryos are morphologically the best-looking and appear to be the fastest to divide, essentially because half of them divide directly into three cells and then six cells at the second cleavage, instead of the two and four cells usually observed for diploid eggs (1).

The metabolic approach of embryo quality was achieved by sampling the culture medium to identify embryo secretions or consumption of particular metabolites. Although degenerating embryos show much lower pyruvate uptake rates than healthy embryos, the possible usefulness of this method for assessing embryo viability is still under discussion (3). In the same fashion, among developing embryos, no evident correlation exists between, on the one hand, glucose metabolic turnover and, on the other hand, the morphological quality of embryos or their apparent rate of cleavage in culture (4). The metabolic approach is therefore disappointing, essentially because embryonic metabolic exchanges are very low and only become easily detectable at

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the blastocyst stage (a long time after the genomic activation occurring at the four- to eight-cell stage). Reliable, sensitive, and elaborate techniques are therefore required.

As noninvasive methods were found to be of limited value, investigators turned to a second method consisting in the dissection of cells or pieces of tissue from embryos, which are then used for preimplantation diagnosis before transfer: this is the invasive approach.

Most important is the detection of genetic or cytogenetic defects in the early embryo. All around the world, basic research on chromosome abnormalities of oocytes and embryos obtained after IVF using a technique of fixation destroying the egg revealed in the last few years that chromosome anomalies represent the major cause of embryonic loss during the pre- and perimplantation period. An average of 26% of the oocytes, 8% of the fertilizing spermatozoa, and 29% of the resulting embryos carry a chromosome abnormality occurring after meiotic or mitotic nondisjunctions, polyploidy, or parthenogenetic activation (5,6). If 25% of these can be (and must be) diagnosed the day after insemination by observing pronuclei, the great majority is impossible to recognize. Moreover, as chromosome anomalies do not interfere with embryonic development during the first 2 days of culture, good-looking embryos could carry lethal anomalies.

It is essential rapidly to diagnose and prevent genetic and cytogenetic diseases at the preimplantation stage. Embryo sexing is technically easy because it involves a single chromosome (the Y chromosome) and, consequently, a single probe. It will soon be available for prevention of sex-linked diseases, which is a good thing, but on the other hand, it is highly likely to be used—or misused?—for personal convenience purposes.

The legitimacy of embryo sexing is in fact the heart of the matter. All over the world, ethical committees debate about sexing with the risk of a prohibition which could include genetic diagnosis as well. If genetic diagnosis is carried out in the same framework as antenatal diagnosis, it will probably be accepted. Conversely, embryo sexing, done essentially for convenience, could be discussed. It is to be sincerely hoped that nothing will interfere with a better knowledge and evaluation of embryo quality and sexing, for the benefit of infertile couples and couples at risk.

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